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# Zwitterion-Initiated Hydroboration of Alkynes and Styrene

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**Abstract:** The hydroboration of alkynes and styrene with HBpin has been developed using tris(pentafluorophenyl)borane ( $\text{B}(\text{C}_6\text{F}_5)_3$ ) as the initiator of catalysis. The hydroboration is proposed to be initiated by Lewis acid activation of the alkyne by ( $\text{B}(\text{C}_6\text{F}_5)_3$ ) to form a highly reactive zwitterionic species which subsequently react with HBpin to give the alkenyl boronic ester. This zwitterion has also showed potential to be a competent catalyst for the hydroboration of styrene. The zwitterionic intermediate is analogous to that proposed in the Piers borane-catalysed hydroboration and 1,1-carboboration of alkynes with  $\text{B}(\text{C}_6\text{F}_5)_3$ .

**Keywords:** Zwitterion; hydroboration; main-group chemistry; homogeneous catalysis; alkyne

Organoboron species are key building blocks in organic synthesis, and thus numerous methods have been developed for the synthesis of bench-stable boronic esters.<sup>[1–6]</sup> The uncatalysed hydroboration of alkenes and alkynes represents the simplest method for the preparation of alkyl- and alkenyl boronic esters. However, and unlike boranes, boronic esters suffer from an inherent lack of reactivity towards alkenes and alkynes. Thus, transition metal-<sup>[7]</sup> and main group-catalysed<sup>[8]</sup> hydroboration reactions have risen to the fore. Stephan reported the hydroboration of alkynes catalysed by Piers borane [ $\text{HB}(\text{C}_6\text{F}_5)_2$ ] (Scheme 1, A). Catalysis was proposed to be initiated by alkyne hydroboration with  $\text{HB}(\text{C}_6\text{F}_5)_2$  and a subsequent hydroboration of the generated alkenyl borane by HBpin to form the active catalyst, a 1,1-diborylated species (**I**).<sup>[9]</sup>

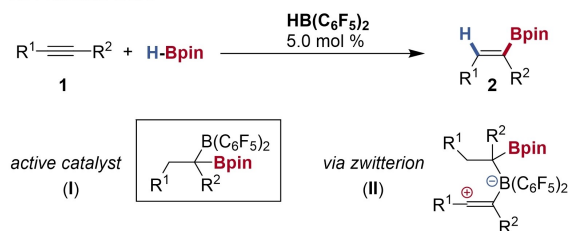
The 1,1-diboryl species (**I**) was proposed to activate a further molecule of alkyne to give a zwitterion (**II**) and undergo a concerted 1,2-hydroboration with HBpin to give the product and regenerate the catalyst (**I**).

The 1,1-carboboration of alkynes is a well-established method for the preparation of alkenyl boranes **3** (Scheme 1, B).<sup>[10]</sup> Here, the strong Lewis acid  $\text{B}(\text{C}_6\text{F}_5)_3$  is proposed to react with a stoichiometric amount of alkyne to generate a zwitterionic intermediate (**III**). This undergoes a Fritsch-Buttenberg-Wiechell rearrangement<sup>[11]</sup> to give the alkenyl borane **3**. The similarity between the 1,1-carboboration intermediate (**III**) and the catalyst structure proposed by Stephan for alkyne hydroboration (**II**) led us to question if any crossover was possible between these two chemistries and that of wider frustrated Lewis-pair-chemistry.<sup>[12]</sup>

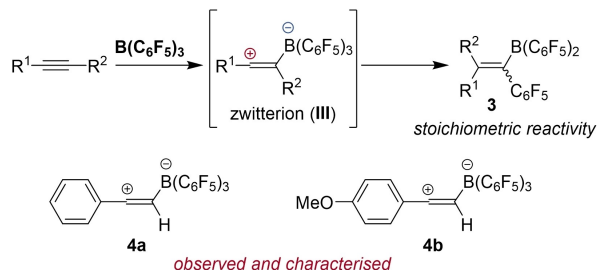
Our recent isolation and characterisation of the zwitterionic intermediate in 1,1-carboboration allowed us to directly explore the potential for divergent reactivity of this species and direct reactivity towards hydroboration, where the role of the zwitterion has not been experimentally established (Scheme 1, C).<sup>[13]</sup>

Using the zwitterion generated from phenyl acetylene **4a**, we began investigating the catalytic activity of these for the hydroboration of alkynes. Reaction of zwitterion **4a** (< 10 mol%) with phenyl acetylene in the presence of HBpin gave the hydroboration product in excellent yield, so confirming the catalytic potential of the zwitterion (see SI, S–R1). In order to simplify the procedure, the zwitterion was generated *in situ* by the reaction of  $\text{B}(\text{C}_6\text{F}_5)_3$  with the alkyne substrate (as confirmed by specific colour change). Essentially allowing the direct use of  $\text{B}(\text{C}_6\text{F}_5)_3$  as a pre-catalysts. Using  $\text{B}(\text{C}_6\text{F}_5)_3$  (20 mol%) in the presence of 1-octyne and pinacolborane gave complete conversion of the starting material to the

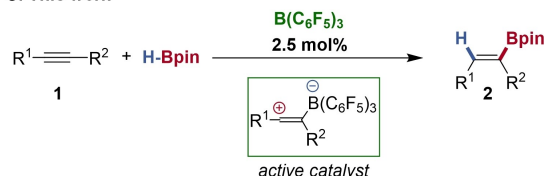
## A: Previous work



## B: Zwitterion intermediates



## C: This work



**Scheme 1.** A:  $\text{HB(C}_6\text{F}_5)_2$ -catalysed hydroboration of alkynes. B: 1,1-Carboboration and characterised zwitterionic intermediates. C: This work.

alkenyl boronic ester in excellent isolated yield, and with full control of regioselectivity (Table 1). While the use of different boron Lewis acids promoted alkyne hydroboration, the activity of these catalysts was significantly lower than of  $\text{B(C}_6\text{F}_5)_3$  (see SI, Table S1). We assessed various reaction parameters using  $\text{B(C}_6\text{F}_5)_3$  as a pre-catalyst to determine the optimal reaction conditions (see SI, Tables S2–S7), and explored the substrate scope of the hydroboration with a variety of alkynes using 2.5 mol% of  $\text{B(C}_6\text{F}_5)_3$  and 1.1 eq. of pinacolborane.

Terminal alkyl- and aryl-substituted alkynes all underwent successful hydroboration (**2a–2k**), the alkyl substituent steric parameters had little effect on catalytic activity with primary (**2a**), secondary (**2b**), tertiary (**2c**) groups all showing equal reactivity. Halide- and silyl-substituents (**2e–2f**) were tolerated under the reaction conditions showing the potential for further orthogonal functionalisation of the products. Chemoselective alkyne hydroboration was observed in the presence of an alkene (**2d**).

Variation of the electronic character of the alkyne aryl substituent again showed that catalytic activity was maintained across arenes bearing either electron-donating (**2h**) or electron-withdrawing (**2i–2j**) substituents. Finally, we explored the reactions of more

**Table 1.** Scope of alkyne hydroboration. Reaction conditions:  $\text{B(C}_6\text{F}_5)_3$  (2.5 mol%), toluene, 2 h, 60 °C. Isolated yields reported.<sup>[a]</sup> Obtained as mixture of regioisomers. Ratio of regioisomers in parentheses. Major regioisomer shown.

$\text{R}^1\text{—C}\equiv\text{C—R}^2 + \text{H-Bpin} \xrightarrow[\text{toluene, 60 °C, 2h}]{\text{B(C}_6\text{F}_5)_3 \text{ 2.5 mol \%}} \text{R}^1\text{—CH=CH—R}^2\text{-Bpin}$		
1		2
 2a 84%	 2b 76%	 2c 63%
 2d 83%	 2e 72%	 2f 68%
 2g 73%	 2h 82%	 2i 86%
 2j 83%	 2k 87%	 2l 43%
 2m 92% (9:1) <sup>a</sup>	 2n 93%	 2o 68% (9:1) <sup>a</sup>

challenging internal alkynes. Symmetrical alkynes with both aryl- (**2l**) and alkyl substituents (**2n**) underwent hydroboration in moderate to good yield and even unsymmetrical disubstituted alkynes were converted to the alkenyl boronic esters with good regioselectivity (9:1) using this protocol (**2m**, **2o**).

Having established a protocol for alkyne hydroboration, we investigated the role of the zwitterion in catalysis. To rule out the formation of Piers borane under reaction conditions, a stoichiometric reaction of  $\text{B(C}_6\text{F}_5)_3$  with HBpin was carried out with only borane decomposition, along with concurrent  $\text{H}_2$  generation,

observed by *in situ*  $^{11}\text{B}$  and  $^1\text{H}$  NMR (Scheme 2, A).<sup>[14]</sup> The diazabicyclo[2.2.2]octane (DABCO) adduct **3** of the zwitterion **4a** was tested for catalytic activity in the hydroboration of phenyl acetylene with no conversion observed at 2.5 mol% loading and only 15% conversion at 10 mol% loading (Scheme 2, B). Presumably the strong binding of DABCO essentially quenches the Lewis acidity of adduct **4a** and that DABCO binding is effectively irreversible under these conditions.

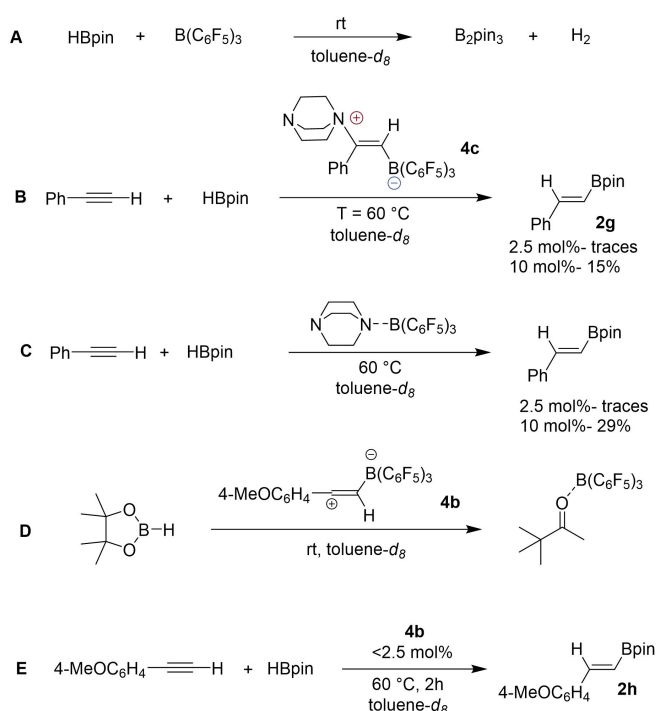
To clarify the role of the Lewis base we tested the DABCO– $\text{B}(\text{C}_6\text{F}_5)_3$  adduct for catalytic activity under our optimised reaction conditions (Scheme 2, C). No catalysis was observed under standard reaction conditions and only when the catalyst loading was increased was catalytic activity observed, albeit with much reduced yield of the alkenyl boronic ester. Hydride shift between HBpin and  $\text{B}(\text{C}_6\text{F}_5)_3$ <sup>[15]</sup> and an increase in deleterious side-reactions was observed (see SI, S–R5). The addition of DABCO thus inhibits catalysis both by coordination to any free  $\text{B}(\text{C}_6\text{F}_5)_3$ , but also by trapping any zwitterion as the catalytically inactive DABCO adduct **4c**.

As the *para*-methoxy substituted zwitterion **4b** exhibited increased thermal stability compared to the unsubstituted parent compound, we next investigated catalyst turnover using this species. However, stoichiometric studies were hampered by pinacol

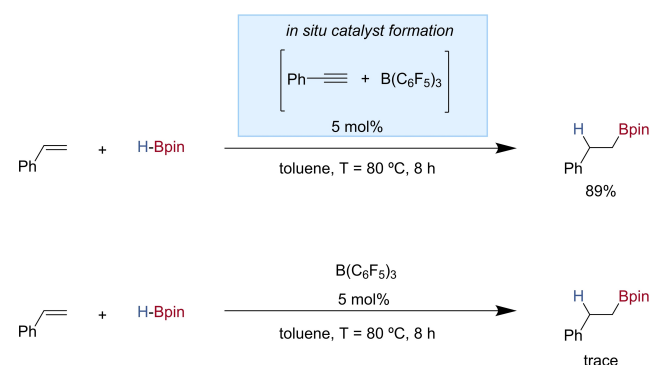
rearrangement<sup>[16]</sup> of the dioxaborolane (HBpin) diol, presumably mediated by the high Lewis acidity of **4b** (Scheme 2, D and see SI, S–R6).  $\text{BH}_3$  was not observed under these conditions, but an unobserved catalytic role cannot be ruled out.<sup>[8k]</sup> However, when sub-stoichiometric loading of zwitterion **4b** was used, no pinacol rearrangement was observed. Using the *para*-methoxy substituted zwitterion **4b** as the catalyst, generated *in situ* from *para*-methoxyacetylene and  $\text{B}(\text{C}_6\text{F}_5)_3$  prior to HBpin addition, successful hydroboration was observed to give the alkenyl boronic ester **2h** (80%) within 2 hours (Scheme 3, E). Based on these experiments the reaction is proposed to proceed by Lewis acid activation of the alkyne to form a highly reactive zwitterion. Subsequent interaction of this species with pinacolborane led to the product and catalyst regeneration.

Having established the competence of  $\text{B}(\text{C}_6\text{F}_5)_3$  in initiating catalysis through a zwitterion **4a** for the hydroboration of alkynes, we began to explore its potential in further applications. Recently, Oestreich and co-workers reported a detailed analysis of the difference in catalytic behavior of  $\text{B}(\text{C}_6\text{F}_5)_3$  and  $\text{B}(3,5\text{-F}_3\text{C-C}_6\text{H}_3)_3$ .<sup>[14]</sup> While the stronger Lewis acid  $\text{B}(3,5\text{-F}_3\text{C-C}_6\text{H}_3)_3$  was able to promote the hydroboration of alkenes, the parent compound  $\text{B}(\text{C}_6\text{F}_5)_3$  was not a competent catalyst. Hence, we questioned if the Lewis acidic zwitterion, formed by interaction between phenylacetylene and  $\text{B}(\text{C}_6\text{F}_5)_3$ , would be an effective catalyst for this transformation. Formation of a sub-stoichiometric amount of the zwitterion **4a** *in situ* by mixing phenyl acetylene and  $\text{B}(\text{C}_6\text{F}_5)_3$  (5 mol%) in the presence of styrene and pinacolborane led to complete conversion of styrene to give the alkyl boronic ester in excellent yield, and with complete control of regioselectivity (Scheme 3). Performing the reaction without any added alkyne, so preventing zwitterion **4a** formation, resulted only in trace amounts of the product, in accordance with Oestreich and co-workers, confirming the pivotal role of the alkyne and zwitterion **4a**.

In conclusion we have demonstrated that the role of  $\text{B}(\text{C}_6\text{F}_5)_3$  in hydroboration catalysis can be more



**Scheme 2.** Mechanistic Studies. A: Reaction of  $\text{B}(\text{C}_6\text{F}_5)_3$  and HBpin. B: Catalysis using zwitterion **4c**. C: Catalysis using zwitterion DABCO– $\text{B}(\text{C}_6\text{F}_5)_3$  adduct. D: Zwitterion **4b** mediated pinacol rearrangement of HBpin. E: Hydroboration catalysis using zwitterion **4b**.



**Scheme 3.** Zwitterion-catalysed hydroboration of styrene.

complex than immediately apparent. In the presence of an alkyne, a zwitterionic intermediate **4** is formed and subsequently acts as a catalyst for the hydroboration reaction. This zwitterion is a strong enough Lewis acid to catalyze the hydroboration of alkenes and thus may offer a potential route to explore further reactivity of the archetypal boron Lewis acid.

## Experimental Section

### General procedure for hydroboration reaction:

The alkyne (0.75 mmol) was added to a solution of  $\text{B}(\text{C}_6\text{F}_5)_3$  (0.0187 mmol, 9.6 mg) in toluene (0.75 mL) and HBpin (0.82 mmol, 0.120 mL) was then added at room temperature. The reaction mixture was stirred for 2 hours at 60°C. The mixture was filtered through a short pad of silica, and the product was purified by flash chromatography.

For further details (NMR spectra, optimization and substrate isolation) please see the supporting information.

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## References


- [1] K. Burgess, M. J. Ohlmeyer, *Chem. Rev.* **1991**, *91*, 1179–1191.
- [2] G. J. Irvine, M. J. G. Lesley, T. B. Marder, N. C. Norman, C. R. Rice, E. G. Robins, W. R. Roper, G. R. Whittell, L. J. Wright, *Chem. Rev.* **1998**, *98*, 2685–2722.
- [3] H. Chen, S. Schlecht, T. C. Semple, J. F. Hartwig, *Science* **2000**, *287*, 1995 LP-1997.
- [4] E. R. Burkhardt, K. Matos, *Chem. Rev.* **2006**, *106*, 2617–2650.
- [5] A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412–443.
- [6] E. C. Neeve, S. J. Geier, I. a. I. Mkhalid, S. A. Westcott, T. B. Marder, *Chem. Rev.* **2016**, *116*, 9091–9161.
- [7] a) I. a. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2009**, *110*, 890–931; b) L. Zhang, D. Peng, X. Leng, Z. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 3676–3680; *Angew. Chem.* **2013**, *125*, 3764–3768; c) J. V. Obligacion, J. M. Neely, A. N. Yazdani, I. Pappas, P. J. Chirik, *J. Am. Chem. Soc.* **2015**, *137*, 5855–5858; d) J. V. Obligacion, P. J. Chirik, *Nat. Rev. Chem.* **2018**, *2*, 15–34.
- [8] a) K. Revunova, G. I. Nikonov, *Dalton Trans.* **2015**, *44*, 840–66; b) C. C. Chong, R. Kinjo, *ACS Catal.* **2015**, *5*, 3238–3259; c) M. S. Hill, D. J. Liptrot, C. Weetman, *Chem. Soc. Rev.* **2016**, *45*, 972–988; d) J. S. McGough, S. M. Butler, I. a. Cade, M. J. Ingleson, *Chem. Sci.* **2016**, *7*, 3384–3389; e) A. Bismuto, S. P. Thomas, M. J. Cowley, *Angew. Chem. Int. Ed.* **2016**, *55*, 15356–15359; *Angew. Chem.* **2016**, *128*, 15582–15585; f) V. A. Pollard, S. A. Orr, R. McLellan, A. R. Kennedy, E. Hevia, R. E. Mulvey, *Chem. Commun.* **2018**, *54*, 1233–1236; g) A. Bismuto, M. J. Cowley, S. P. Thomas, *ACS Catal.* **2018**, *8*, 2001–2005; h) N. W. J. Ang, C. S. Buettner, S. Docherty, A. Bismuto, J. R. Carney, J. H. Docherty, M. J. Cowley, S. P. Thomas, *Synth.* **2018**, *50*, 803–808; i) M. W. Stanford, A. Bismuto, M. J. Cowley, *Chem. Eur. J.* **2020**, *26*, 9855–9858; j) A. D. Bage, K. Nicholson, T. A. Hunt, T. Langer, S. P. Thomas, *ACS Catal.* **2020**, *22*, 13479–13486; k) A. D. Bage, T. A. Hunt, S. P. Thomas, *Org. Lett.* **2020**, *22*, 11, 4107–4112.
- [9] M. Fleige, J. Möbus, T. vom Stein, F. Glorius, D. W. Stephan, *Chem. Commun.* **2016**, *52*, 10830–10833. Please note,  $\text{B}(\text{C}_6\text{F}_5)_3$  was also used as a pre-catalysts for the hydroboration of 4-methoxyphenyl acetylene.
- [10] G. Kehr, G. Erker, *Chem. Commun.* **2012**, *48*, 1839–1850.
- [11] a) B. Wrackmeyer, *Coord. Chem. Rev.* **1995**, *145*, 125–156; b) B. Wrackmeyer, S. Bayer, W. Milius, E. V. Klimkina, *J. Organomet. Chem.* **2018**, *865*, 80–88.
- [12] For relevant reviews about FLP chemistry see: a) D. W. Stephan, *J. Am. Chem. Soc.* **2015**, *137*, 10018–10032; b) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2015**, *54*, 6400–6441; *Angew. Chem.* **2015**, *127*, 6498–6541; c) D. W. Stephan, *Acc. Chem. Res.* **2015**, *48*, 306–316; d) J. Paradies, *Coord. Chem. Rev.* **2019**, *380*, 170–183; e) J. Lam, K. M. Szkop, E. Mosafari, D. W. Stephan, *Chem. Soc. Rev.* **2019**, *48*, 3592–3612; f) V. Iashin, K. Chernichenko, I. Pápai, T. Repo, *Nat. Chem.* **2013**, *5*, 718–722; g) T. Mahdi, D. W. Stephan, *Angew. Chem.* **2013**, *125*, 12644–12648; *Angew. Chem. Int. Ed.* **2013**, *52*, 12418–12421; h) V. Desrosiers, C. Z. Garcia, F. Fontaine, *ACS Catal.* **2020**, *10*, 11046–11056.
- [13] A. Bismuto, G. S. Nichol, F. Duarte, M. J. Cowley, S. P. Thomas, *Angew. Chem.* **2020**, *132*, 12831–12835.
- [14] Q. Yin, S. Kemper, H. F. T. Klare, M. Oestreich, *Chem. Eur. J.* **2016**, *22*, 13840–13844.
- [15] C. J. Lata, C. M. Crudden, *J. Am. Chem. Soc.* **2010**, *132*, 131–137.
- [16] M. Uzelac, K. Yuan, M. J. Ingleson, *Organometallics* **2020**, DOI 10.1021/acs.organomet.0c00086.



## COMMUNICATIONS

### Zwitterion-Initiated Hydroboration of Alkynes and Styrene

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